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Editorials

Brief Rapid Communications

Clinical Investigation and Reports

Prevention of Cardiovascular Disease*

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Coronary Sinus Pacing Prevents Induction of Atrial Fibrillation

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Background Atrial fibrillation (AF) is due to reentry, and its incidence has been shown to decrease after dual-site atrial or biatrial pacing. We investigated whether a simpler pacing approach via the distal coronary sinus (CSd) could eliminate AF inducibility by high right atrial (HRA) extrastimuli (APDs). We based our hypothesis on our previous observation that AF inducibility by HRA APDs was associated with conduction delays to the posterior triangle of Koch, whereas AF was never induced with CSd APDs, which were associated with minimal intra-atrial conduction delays.

Methods and Results Programmed electrical stimulation was performed from the high right atrium and CSd, and bipolar recordings were obtained from the high right atrium, His bundle, posterior triangle of Koch, and coronary sinus. In 13 patients (age, 44±18 years), AF was reproducibly induced with a critically timed HRA APD (220±22 ms) delivered during HRA pacing. AF was not induced in any of the patients when HRA APDs were delivered during CSd pacing at the same critical coupling intervals. Coronary sinus APDs delivered during HRA pacing also were not associated with AF induction. The APD coupling interval measured at the posterior triangle of Koch during CSd pacing was significantly prolonged compared with the one measured during HRA pacing and AF induction (381±58 versus 263±37 ms; $P<.0001$).

Conclusions We propose that CSd pacing suppresses the propensity of HRA APDs to induce AF by limiting their prematurity at the posterior triangle of Koch and not allowing local conduction delay and local reentry to occur. (*Circulation.* 1997;96:1893-1898.)

Key Words • pacing • fibrillation • reentry

Atrial fibrillation constitutes a significant health issue afflicting ≈1 000 000 Americans, with an incidence up to 4% in people older than 60 years and up to 13% in those older than 70 years.[1] Although there are a variety of antiarrhythmic drugs that may help maintain sinus rhythm in patients with paroxysmal AF, the ultimate outcome is usually the establishment of chronic AF and its associated morbidities. To prevent recurrences of AF, investigators have turned to radiofrequency ablations to create linear intra-atrial lesions and lines of block[2] or have applied permanent pacing techniques. In the latter category, the impetus for investigating pacing modalities has been provided by retrospective[3-5] and prospective[6] studies that have conclusively shown that atrial or dual-chamber pacing reduces the occurrence of AF compared with ventricular pacing in patients with sick sinus syndrome. Recent work has suggested that dual-site atrial[7] or biatrial[8,9] pacing can suppress the recurrence of drug-refractory AF or atrial flutter. In addition, there is preliminary evidence that simultaneous right and left atrial pacing increases atrial refractoriness and decreases the intra-atrial conduction delay after a low right atrial ectopic beat.[10]

Our previous work[11] demonstrated that HRA APDs, which induced AF, were associated with nonuniform anisotropic conduction in the region of the posterior triangle of Koch, suggesting that local reentry mechanisms may be involved in AF initiation. It should be noted that AF was only observed with HRA APDs delivered during HRA pacing and was never seen with CSd APDs delivered during CSd pacing. Furthermore, CSd extrastimulus testing was associated with minimal intra-atrial conduction delays and minimal prolongation of atrial relative refractoriness.

In the present work, we postulated that prevention of early activation of the posterior triangle of Koch would prohibit AF induction by critically coupled HRA APDs. We therefore tested whether CSd pacing could limit the achievable coupling intervals at the posterior triangle of Koch during HRA APDs and prevent AF.

Methods

In 31 consecutive patients referred to our laboratory for arrhythmia evaluation, comprehensive electrophysiological studies were performed as described below.

Catheter Positioning

A 6F, 5-mm-spaced quadripolar electrode catheter was placed at the HRA; a 7F, steerable 2/5/2-mm-spaced, 2-mm-tip quadripolar electrode catheter was positioned at the posterior triangle of Koch at the level of the CS ostium (P_1 location, as previously described[12]); a 6F, 2-mm-spaced decapolar electrode catheter was placed in the AV junction along the tendon of Todaro and positioned to obtain the largest His bundle deflection in the distal electrode pair; and a 5-mm-spaced decapolar electrode catheter was placed in the CS with the proximal electrode at the ostium. A schematic presentation of the catheter positions is shown in Fig 1.

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Selected Abbreviations and Acronyms

AF = atrial fibrillation
APD = atrial premature depolarization
CS = coronary sinus
CSd = distal coronary sinus
ERP = effective refractory period
HRA = high right atrium (atrial)

Stimulation Parameters

The distal electrode pairs of the HRA and CS catheters were used for bipolar stimulation. The stimulus output had a pulse width of 2 ms and was set at twice the diastolic threshold. Threshold values ranged from 0.2 to 1.0 mA for the HRA stimulation and from 0.5 to 1.5 mA for the distal CS stimulation. Particular care was taken to ensure continuous capture of the atrial tissue when threshold values were determined.

Recording Parameters

Bipolar recordings filtered at 30 to 500 Hz were obtained from all intra-atrial sites. An analog-to-digital sampling rate of 1 kHz was applied before digital storage and analysis. Measurements were performed at a sweep speed of 200 mm/s using electronic calipers and by maintaining the same gain setting in all recordings. To ensure reproducibility of the measurements, tracings were analyzed by two investigators. The difference between independent measurements never exceeded 10 ms.

Stimulation Protocol

Programmed electrical stimulation was performed only during normal sinus rhythm. Programmed single APDs at increasing prematurity were delivered during HRA pacing at drive cycles of 600 and 450 ms until AF was induced or until the atrial ERP was encountered. Single HRA APDs were then delivered during CSd-paced drives of 600 and 450 ms until the HRA ERP was reached. Similarly, single CSd APDs were delivered during HRA-paced drives of 600 and 450 ms until the CSd ERP was reached.

Statistics

The statistical analysis was based on the paired t test. The null hypothesis was rejected at a value of $P<.05$. Data are expressed as mean±SD.

Results

Of 31 patients, AF was induced in 13 (age, 44±18 years; patient characteristics shown in Table 1). AF was induced only after an HRA-paced drive and a single HRA APD at a mean critical coupling interval of 220±22 ms (range, 170 to 250 ms). The induction of AF was reproduced up to three times at the same critical APD coupling interval. The duration of the induced AF ranged between 20 seconds and 15 minutes, and in all but one instance, AF terminated spontaneously. In that single case, AF was sustained after a second reinduction, and the patient was electrically cardioverted to sinus rhythm. An example of AF induction after a critically coupled HRA APD is presented in Fig 2. At the critical HRA APD coupling intervals that induced AF, the mean APD coupling interval achieved at the posterior triangle of Koch was 263±37 ms.

During normal sinus rhythm, single HRA APDs were again delivered after a CSd-paced drive. The stimulation proceeded until the HRA ERP was reached. At the critical HRA APD coupling intervals that previously induced AF during HRA pacing, AF was not seen during CS pacing in any of the 13 patients. At shorter HRA APD coupling intervals during CS pacing, the ERP was encountered

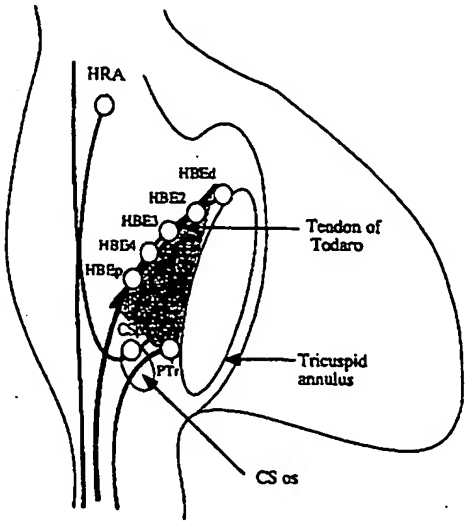

FIG 1. Schematic of catheter location during the study (see text for details). HBE indicates His bundle electrogram; HBEd, distal HBE; HBEp, proximal HBE; PTr, posterior triangle of Koch; and CSp, proximal coronary sinus.

TABLE 1. Clinical Characteristics of All 13 Patients in Whom AF Was Induced

Patient	Sex	Age, y	Echo Findings	Symptoms	Diagnosis
1	Male	54	Normal	Palpitations	RVOT VT
2	Male	41	Normal	Palpitations	AVNRT, CMT
3	Female	67	Normal	Palpitations	PAF
4	Female	32	RHD, MS, AI	Palpitations	AVNRT, AFI
5	Female	65	Normal	Palpitations	PAF
6	Male	42	LVH	Presyncope	VT
7	Male	73	Normal	Syncope	PAF
8	Male	27	Normal	Palpitations	PAF
9	Male	36	Normal, PFO	Palpitations	AFI
10	Male	16	Normal	Palpitations	PAF
11	Male	43	Normal	Palpitations	AFI
12	Male	54	EF 0.25	Palpitations	AVNRT
13	Male	18	Normal	Palpitations	AVNRT

RVOT indicates right ventricular outflow tract; VT, ventricular tachycardia; AVNRT, AV nodal reentrant tachycardia; CMT, circus movement tachycardia via a concealed bypass tract; PAF, paroxysmal AF; RHD, rheumatic heart disease; MS, mitral stenosis; AI, aortic insufficiency; AFI atrial flutter; LVH, left ventricular hypertrophy; PFO, patent foramen ovale; and EF, ejection fraction.

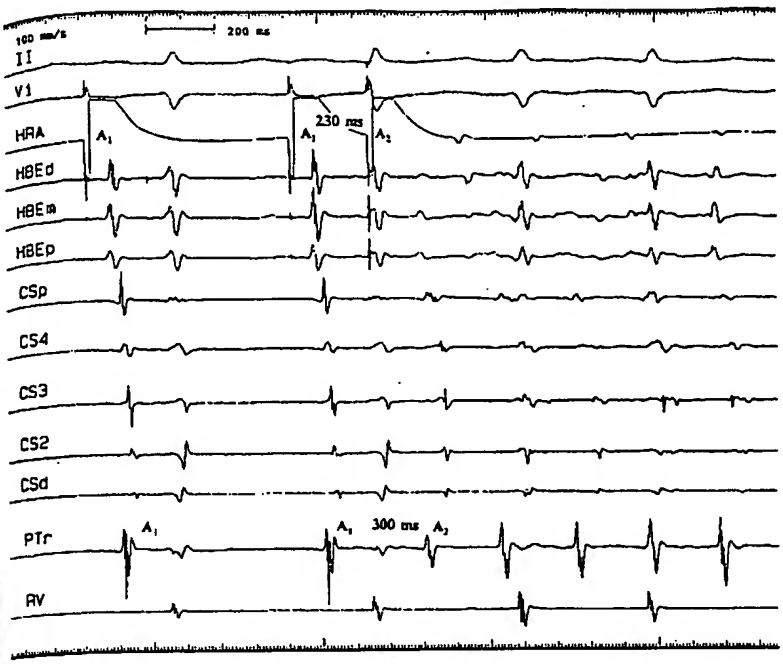

FIG 2. Surface (leads II and V_1) and intracardiac electrograms from a patient during initiation of AF. During an HRA-paced drive at 600 ms, an HRA APD is delivered at a coupling interval of 230 ms (A1-A2 at HRA) and initiates AF. The corresponding coupling interval at the posterior triangle of Koch is 300 ms (A1-A2 at PTr). HBE indicates His bundle electrogram; HBEd, distal HBE; HBEm, mid-HBE; HBEp, proximal HBE; CSp, proximal coronary sinus; PTr, posterior triangle of Koch; and RV, right ventricle.

without prior AF initiation. Fig 3 presents AF prevention by CSd pacing in the patient shown in Fig 2. As during AF induction, the critically coupled HRA APD during CS pacing was repeatedly delivered to demonstrate reproducibility of the findings. At critical HRA APD coupling intervals, the mean coupling interval at the posterior triangle of Koch during CS pacing was 381±58 ms, significantly longer than the one achieved during HRA pacing and AF induction (263±37 ms; $P<.0001$; Table 2). Fig 4 displays schematically the coupling intervals achieved at the posterior triangle of Koch in each patient during HRA APDs. It is apparent that in each patient, CS pacing was associated with posterior triangle coupling intervals that were longer by 30 to 170 ms than intervals seen during HRA pacing.

In 7 of the 13 patients with AF induction, we also performed CS extrastimulus testing during HRA pacing. CSd APDs were delivered until local refractoriness was reached. At the most premature CSd APD able to capture the CS during HRA pacing, the mean coupling interval at the posterior triangle of Koch was 340±51 ms, and AF was not seen. Figs 5, 6, and 7 show all three stimulation protocols in the same patient. Fig 5 shows that during the HRA-paced/HRA APD protocol, an HRA APD at 230 ms induced AF. Fig 6 shows that during the CS-paced/HRA APD protocol, an HRA APD coupled at 230 ms during CS pacing was unable to induce AF. Finally, Fig 7 shows that during the HRA-paced/CS APD protocol, there was no AF induction at the most premature APD capturing the CS.

Discussion

Little doubt remains that AF constitutes a reentrant arrhythmia. Moe and coworkers[13,14] initially proposed

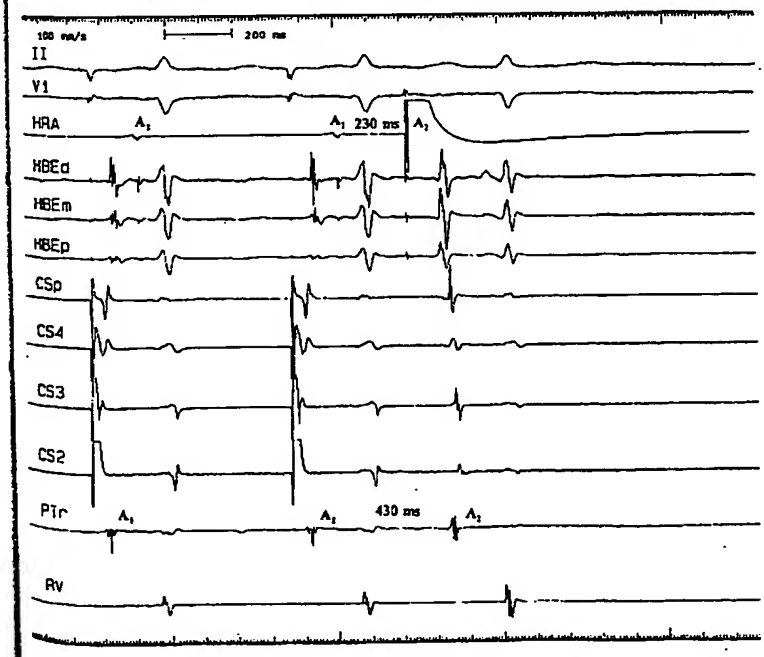

FIG 3. Surface and intracardiac electrograms demonstrating AF prevention in the same patient as in Fig 2. During a CSd-paced drive at 600 ms, an HRA APD is delivered at a coupling interval of 230 ms (A1-A2 at HRA), which depolarizes the atria but does not induce AF. The corresponding coupling interval at the posterior triangle of Koch is 430 ms (A1-A2 at PTr). The CSd electrogram is not displayed due to pacing artifact. Abbreviations as in Fig 2.

TABLE 2. APD Coupling Intervals at HRA and Posterior Triangle of Koch

	AF Induction (HRA Pacing)	AF Prevention (CSd Pacing)
A1-A2 (HRA)	220±22ms	220±22ms
A1-A2 (Post T)	263±37ms	381±58ms

Post T indicates posterior triangle of Koch.
Values are mean±SD HRA APD coupling intervals measured at the HRA and the posterior triangle of Koch during induction and prevention of AF.

the multiple wavelet hypothesis that introduced the notion of AF being the result of multiple reentrant wavelets wandering around anatomic or electrical barriers. These observations were corroborated by the work of Allessie and coworkers,[15-17] who further demonstrated that in the face of short refractory periods and slow conduction, reentry is permissible even in small areas of conduction block. It is possible, therefore, that a small intra-atrial area of nonuniform anisotropic conduction with a short refractory period may allow the formation of reentrant circuits that initiate AF.

Our previous work[11] suggested that the posterior triangle of Koch may be a region of anisotropic conduction responsible for AF initiation. Patients with AF inducibility have exhibited increased conduction times to that region and pronounced local conduction delays during HRA stimulation.[11] The notion of a single right atrial APD inducing AF due to possible reentry in the low right atrium led us to the hypothesis that local reentry, and thus AF, will be prevented if the achievable coupling interval at the posterior triangle of Koch during a critical HRA APD is decreased. We propose that this objective can be attained via CSd pacing as follows:

During CSd pacing, the low right atrium is activated before the HRA; therefore, an HRA APD delivered during CSd pacing will activate the posterior triangle of Koch with a longer coupling interval. The sequence of activation during our stimulation protocol is shown schematically in Fig 8. In Fig 8A (HRA-paced drive), the critical HRA APD coupling interval that induces AF

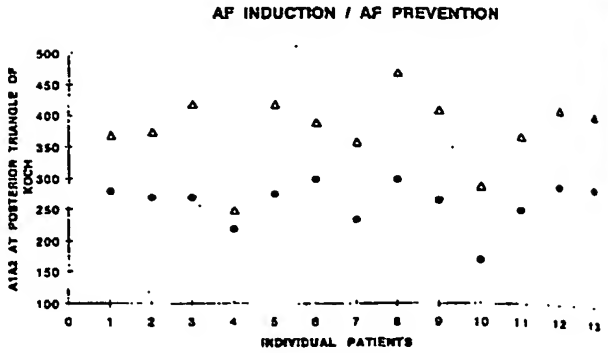

FIG 4. A scatterplot of the individual coupling intervals achieved at the posterior triangle of Koch (A1-A2, in ms) in response to HRA APDs. ●, A1-A2 intervals during HRA-paced drives associated with AF induction. △, A1-A2 intervals during CSd-paced drives not accompanied by AF induction.

produces a certain A1-A2 interval at the posterior triangle. In Fig 8B (CSd-paced drive), an HRA APD at the same critical coupling interval as in 8A produces a longer A1-A2 interval at the posterior triangle, and AF is not initiated.

In 13 patients, AF was reproducibly induced with critically coupled single APDs from the HRA and was reproducibly prevented when equally premature HRA APDs were delivered during CSd pacing. Patients in whom AF was induced did not have a prior history of documented AF. The final diagnosis of paroxysmal AF in some of the patients, as seen in Table 1, was made after the electrophysiological evaluation did not reveal any additional arrhythmias. The small number of patients that we have studied so far does not allow for an association between the readiness of AF induction or prevention and the nature of the underlying cardiac condition. Furthermore, at this point, the clinical relevance of AF induction and prevention during an electrophysiological study is not yet clear. It is important to stress, however, that in every single patient in whom AF

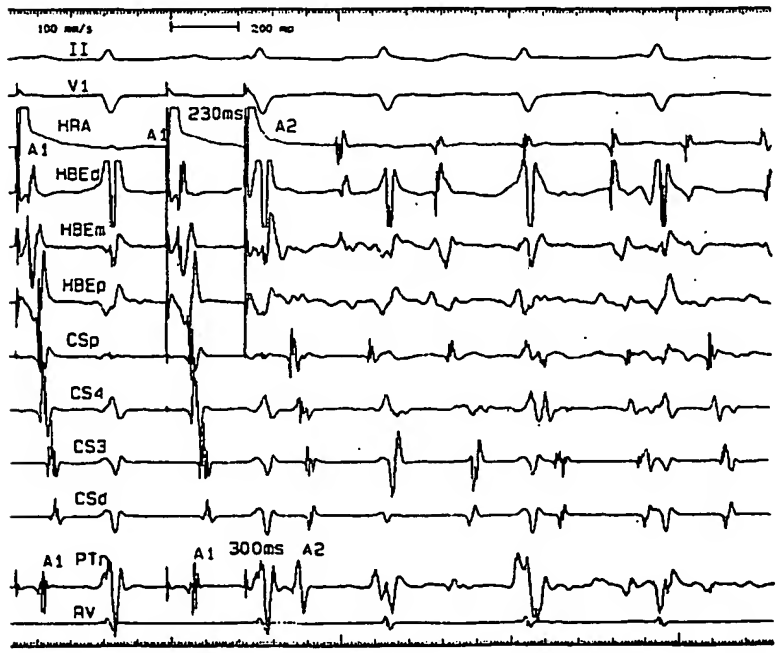

FIG 5. Surface (leads II and V_1) and intracardiac electrograms from a patient during initiation of AF. During an HRA-paced drive at 450 ms, an HRA APD is delivered at a coupling interval of 230 ms (A1-A2 at HRA) and initiates AF. The corresponding coupling interval at the posterior triangle of Koch is 300 ms (A1-A2 at PTr). Abbreviations as in Fig 2.

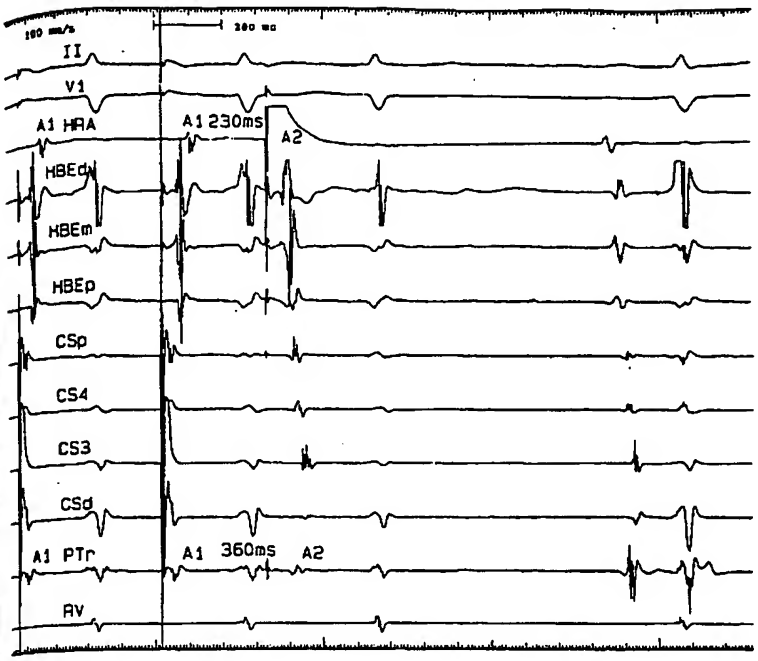

FIG 6. Surface and intracardiac electrograms demonstrating AF prevention in the same patient as in Fig 5. During a CSd-paced drive at 450 ms, an HRA APD is delivered at a coupling interval of 230 ms (A1-A2 at HRA), which depolarizes the atria but does not induce AF. The corresponding coupling interval at the posterior triangle of Koch is 360 ms (A1-A2 at PTr). Abbreviations as in Fig 2.

was induced during HRA APD and HRA pacing, AF was not seen during HRA APD and CS pacing.

The combination of HRA-paced drive and CSd APDs also was not associated with AF induction, and the achievable prematurity at both the HRA and posterior triangle of Koch was far less than the profibrillatory combination of HRA-paced drive/HRA APDs. It is possible that HRA pacing may limit a fibrillatory role of left atrial APDs, but it clearly fails to do so with HRA APDs. In our overall experience presented in this report and elsewhere,[11] CSd pacing followed by either HRA or CSd APDs was never associated with AF induction. Our observations clearly underscore a potential clinical role for CS pacing. Continuous CSd pacing in patients with paroxysmal AF or in patients at high risk for developing AF may reduce the fibrillatory potential of right atrial extrasystoles.

Right atrial and biatrial pacing modes are currently the subjects of intense investigation regarding their role in decreasing the occurrence of AF. The antifibrillatory effect of dual-chamber pacing traditionally has been attributed to improved hemodynamics relative to VVI pacing.[18] Recently, it has been proposed that the need for demand pacing may be unrelated to the antiarrhythmic effect[19] and that simultaneous triggered pacing of both the right and left atria may provide an antifibrillatory effect by preventing conduction delays and by lengthening atrial refractoriness after atrial extrasystoles.[10] The latter report is in agreement with our previous observation[11] that CSd stimulation produced minimal intra-atrial conduction delays and was never associated with AF induction. Prakash et al[20] demonstrated a 56% efficacy in abolishing the profibrillatory potential of

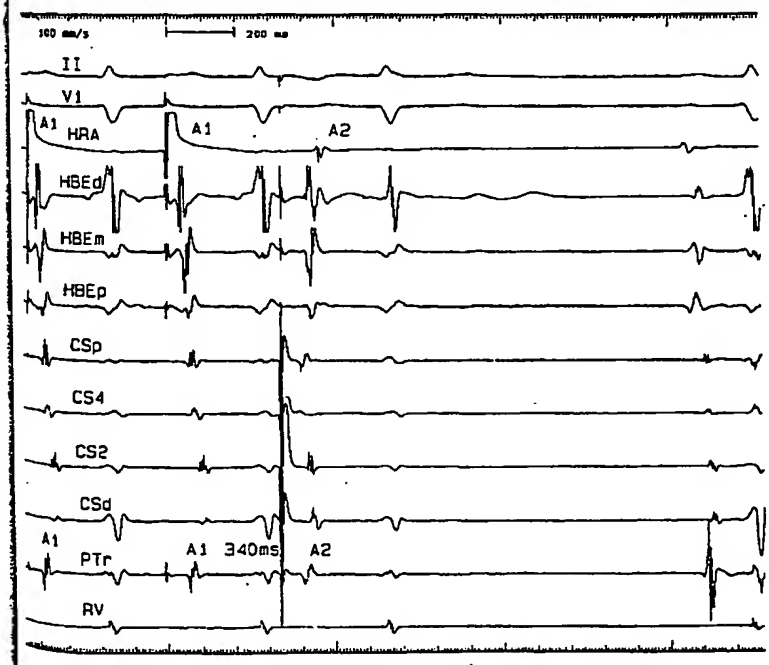

FIG 7. Surface and intracardiac electrograms in the same patient as in Figs 5 and 6. During an HRA-paced drive at 450 ms, the most premature CS APD is shown. The corresponding coupling interval at the posterior triangle of Koch is 340 ms (A1-A2 at PTr) and measures 440 ms at the HRA (A1-A2 at HRA). Abbreviations as in Fig 2.

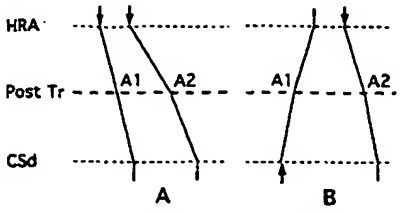

FIG 8. A qualitative ladder diagram displaying the sequence of atrial activation during the stimulation protocols. The arrows denote the sequence of stimulation (HRA-HRA in A; CSd-HRA in B). See text for details. Post Tr indicates posterior triangle of Koch.

HRA extrastimuli by using simultaneous dual-site pacing from the HRA and CS os in patients in whom HRA extrastimuli during HRA pacing alone previously induced AF. The observations above underscore the need for prospective studies comparing biatrial, dual-site right atrial, and CSd pacing, because the required lead systems for the latter are simpler and would be associated with lower morbidity.

In the present report, we have demonstrated that CSd pacing eliminates the propensity of HRA extrasystoles to induce AF. We propose that this is achieved by a decrease in the APD prematurity at the posterior triangle of Koch, further supporting the concept that this region is critical in AF initiation. Our observations also raise the possibility of colliding wave fronts preventing the slowing of conduction and functional block in critical areas of the right atrium. Limitations inherent to the use of catheter-based mapping do not allow us to fully dissect the mechanisms responsible for AF induction and prevention. We have documented premature excitation of the right atrium with nonuniform activation by CSd pacing, but we cannot dissect the role of preexcited right atrial activation or anisotropic conduction of right atrial premature beats because comparable coupling intervals to those initiating AF at the posterior triangle of Koch could never be achieved. Because the atrial preexcitation is inherent to the preventative CS drive, the role of CS influence on nonuniform anisotropic conduction at the triangle of Koch can never be addressed. Additional studies involving high-density mapping of the posterior right and left atria will be necessary to elucidate the exact mechanisms. In addition, future clinical trials may document whether continuous atrial pacing via the CSd can actually decrease the incidence of clinical AF.

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